NOTE: This disposition is nonprecedential.

United States Court of Appeals for the Federal Circuit

TAKEDA PHARMACEUTICAL COMPANY LTD., TAKEDA PHARMACEUTICALS U.S.A., INC., TAKEDA PHARMACEUTICALS AMERICA, INC., TAKEDA IRELAND LIMITED,
Plaintiffs-Appellees

v.

TORRENT PHARMACEUTICALS LTD., TORRENT PHARMA INC.,
Defendants-Appellants

INDOCO REMEDIES LTD.,
Defendant-Appellant

2020-1552, 2020-1598

Appeals from the United States District Court for the District of New Jersey in Nos. 2:17-cv-03186-SRC-CLW, 2:17-cv-07301-SRC-CLW, Judge Stanley R. Chesler.

Decided: February 16, 2021

GREGORY A. CASTANIAS, Jones Day, Washington, DC, argued for plaintiffs-appellees. Also represented by JASON G. WINCHESTER, Chicago, IL; LISAMARIE LOGIUDICE, New

York, NY.

H. KEETO SABHARWAL, Pillsbury Winthrop Shaw Pittman LLP, Washington, DC, argued for defendants-appellants Torrent Pharmaceuticals Ltd., Torrent Pharma Inc. Also represented by CEDRIC CHIA YANG TAN, YUN WEI.

IVAN MICHAEL POULLAOS, Winston & Strawn LLP, Chicago, IL, argued for defendant-appellant Indoco Remedies Ltd. Also represented by ALISON MICHELLE HEYDORN, GEORGE C. LOMBARDI, JOHN REYNOLDS MCNAIR.

Before DYK, MAYER, and CHEN, *Circuit Judges*.

CHEN, *Circuit Judge*.

Torrent and Indoco (collectively, Appellants) appeal from the district court's final judgment on Appellants' invalidity challenges to claims 4 and 12 of U.S. Patent No. 7,807,689, owned by Takeda.[1] *See Takeda Pharm. Co. Ltd. v. Torrent Pharm. Ltd.*, No. 2:17-cv-03186-SRC-CLW, 2020 WL 549594, at *26 (D.N.J. Feb. 4, 2020) (*Takeda*). The claims at issue are directed to alogliptin, a uracil-containing DPP-IV inhibitor useful for treating type II diabetes, and pharmaceutical salts thereof. Following a two-day bench trial and extensive testimony from three different experts, the district court concluded Appellants had failed to prove by clear and convincing evidence that the challenged claims are invalid for either statutory obviousness or non-statutory obviousness-type double patenting. In their appeal, Appellants challenge several different fact

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[1] Torrent refers to Torrent Pharmaceuticals Ltd. and Torrent Pharma Inc. Indoco refers to Indoco Remedies Ltd. Takeda refers to Takeda Pharmaceutical Company Ltd., Takeda Pharmaceuticals U.S.A., Inc., Takeda Pharmaceuticals America, Inc., and Takeda Ireland Limited.

findings by the district court. Even assuming some of those challenges have merit, we discern no clear error in the district court's finding that a skilled artisan would not have been motivated to make Appellants' proposed scaffold and isosteric replacements with a reasonable expectation of success. On that basis, we *affirm*.

DISCUSSION

Relevant to "the assessment of [reasonable] expectation of success" in all three of Appellants' invalidity theories, *Takeda*, 2020 WL 549594, at *11, is the undisputed factual finding that "in the relevant art of pharmaceutical development, very small changes in molecular structure can have dramatic effects on the properties of the molecule," *id.* at *10. Indeed, "the more distantly related two chemical structures are, the less probable it will be that they have the same biological effect." J.A. 33375–76 (Böhm). Against this backdrop, we turn to the details of Appellants' invalidity theories.

A

Torrent presents two obviousness-type double patenting theories using Feng's[2] F162 compound as the lead compound for further modification. First, Torrent argues that a skilled artisan would have found it obvious to replace F162's pyrimidinone scaffold with uracil, citing Böhm and Kim.[3] Böhm discloses that scaffold replacement techniques were known in the prior art as of the relevant priority date. Kim reports that administering uracil lowers blood glucose in an animal model of diabetes but "[does] not

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[2] Feng refers to U.S. Patent No. 7,723,344.

[3] Böhm refers to Böhm *et al.*, "Scaffold Hopping," *Drug Discovery Today: Technologies* 1, No. 3 (December 2004): 217–23. Kim refers to Kim *et al.*, "Anti-diabetic Activity of Constituents of Lycii Fructose," The Journal of Applied Pharmacology 6 (1998): 378–82.

mention DPP-IV or DPP-IV inhibitors or scaffold hopping or the use of uracil as a scaffold." *See Takeda*, 2020 WL 549594, at *27. Collectively, these references, along with other evidence of record, do not demonstrate that uracil was known to possess DPP-IV inhibitory activity or other characteristics desirable in a scaffold for DPP-IV inhibition as of the relevant priority date.[4] Given that Torrent fails to establish that uracil was known at the time of invention to lower blood glucose by inhibiting DPP-IV, or was otherwise understood to be a desirable scaffold for DPP-IV inhibition, we conclude that the district court did not clearly err in finding that a skilled artisan would not have been motivated to replace F162's pyrimidinone scaffold with a uracil scaffold with a reasonable expectation of success.

Second, Torrent contends that a skilled artisan would have been motivated to replace a fluoro-olefin unit in F162's pyrimidinone scaffold with an amide unit. Torrent argues that fluoro-olefin and amide were known isosteres in the prior art, and "[b]ecause the [skilled artisans] are medicinal chemists who are 'always looking for a novel

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[4] At oral argument, Torrent's counsel argued that Kim need not disclose that uracil is a DPP-IV inhibitor because other prior art references of record purportedly teach this feature. *See* Oral Arg. at 8:49–9:30; *id*. at 36:09–36:33. None of the record evidence counsel directed us to discloses that uracil was a known DPP-IV inhibitor. *See, e.g.*, J.A. 33246–347 ("Kanstrup," a PCT publication pertaining to xanthine-based compounds, not uracil); J.A. 33496–715 ("Mark 2004," another patent reference pertaining to xanthine-based compounds); J.A. 1473–74 (an excerpt from Torrent's post-trial briefing stating that "*[x]anthine*-based compounds were known DPP-IV inhibitors" (emphasis added)). Notably, moreover, Torrent's expert agreed at trial that the Kanstrup and Mark 2004 references "do[] not say one word about using a uracil scaffold." J.A. 911–12

compound,' the [skilled artisan] would have been motivated to replace [F162's] fluoro-olefin . . . with its isostere (an amide bond) with a reasonable expectation to develop a new DPP-IV inhibitor." J.A. 1484. We discern no clear error in the district court's contrary holding. Torrent has not identified anything in the prior art that would have motivated a skilled artisan to dispose of F162's fluoro-olefin unit, let alone replace it with an amide, given myriad more conservative and predictable modifications that were available for transforming F162 into a "novel" compound. *See Takeda*, 2020 WL 549594, at *18–19. To the contrary, Torrent's expert conceded at trial that he was unaware of any prior art disclosing this specific modification, despite citing references that taught the opposite modification—replacing an amide unit with a fluoro-olefin unit. J.A. 942–43. Even the reference Torrent cites to establish that fluoro-olefin and amide were known isosteres features fluoro-olefin compounds and is bereft of any suggestion to make the replacement Torrent proposes. J.A. 33349, 33352.

B

As for statutory obviousness, Indoco argues that a skilled artisan would have been motivated to use DCAX as a lead compound and to replace DCAX's xanthine scaffold with uracil because xanthine and uracil are "interchangeab[le]" "naturally occurring nitrogenous bases." *See Takeda*, 2020 WL 549594, at *24. Even assuming, *arguendo*, that the prior art would have motivated a skilled artisan to modify DCAX by replacing its xanthine scaffold with uracil, we agree with the district court that Indoco "failed to show that a [skilled artisan] who did so would have [had] a reasonable expectation of success" with "this particular scaffold replacement." *See id.* at *24–25. The interchangeability references on which Indoco relies do not pertain to DPP-IV inhibitors or diabetes, nor do they, or any other prior art of record, teach substituting an existing xanthine scaffold for uracil, *see* Oral Arg. at 19:32–40 (acknowledging that Wiedeman does not show a xanthine to

uracil swap). Moreover, Indoco's expert, as the district court observed, did not present any testimony or evidence as to the predictability of the resulting properties from replacing DCAX's scaffold with uracil.[5] *See Takeda*, 2020 WL 549594, at *25. We thus decline to disturb the district court's finding that Indoco failed to prove by clear and convincing evidence that a skilled artisan would have been motivated to replace DCAX's xanthine scaffold with uracil with a reasonable expectation of success.

C

Lastly, we address Appellants' contention that the district court materially erred with respect to the level of ordinary skill in the art. Appellants argue that the district court improperly ignored the parties' dispute over whether a skilled artisan must have specific experience developing DPP-IV inhibitors and/or type II diabetes drugs—experience Takeda's expert did not have.[6] This specific experience, Appellants contend, is a material difference insofar

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[5] Unlike Indoco's expert, Takeda's expert addressed this critical issue, testifying that a skilled artisan would not have been able to predict the resulting properties from the "wholesale" replacement of a lead compound's scaffold with uracil. *See* J.A. 1159–60.

[6] At oral argument, Torrent's counsel asserted that the district court's motivation analysis improperly relied on testimony of Takeda's expert to the exclusion of Torrent's expert, specifically referencing a footnote in the opinion below. *See* Oral Arg. at 4:43–6:50 (discussing *Takeda*, 2020 WL 549594, at *12 n.3, which cites the trial transcript at J.A. 1178–80, 910–11). That footnote refers to testimony from both Takeda's *and* Torrent's experts, including testimony from Torrent's expert agreeing that "the Kim reference doesn't say one word about DPP-IV inhibition," J.A. 910–11. Torrent's counsel, moreover, could not identify anything factually inaccurate about the footnote.

as it is critical to the district court's findings regarding motivation and reasonable expectation of success. We disagree.

Rather than ignore the dispute, the district court considered the prior art from *both* perspectives—that of a skilled artisan with and without specific experience with DPP-IV inhibitors or type II diabetes drugs—and concluded that Appellants' had failed to prove invalidity under either definition of a skilled artisan. *See Takeda*, 2020 WL 549594, at *11 (finding that it "need not" resolve whether the specific DPP-IV/type II diabetes experience urged by Appellants was required "because it has no effect on the outcome: even if [Appellants] are correct in this, they still fail to provide invalidity by clear and convincing evidence").

Given the substantive gaps in establishing motivation and reasonable expectation of success identified above, the record supports the district court's conclusion that it would have reached the same outcome under either definition of a skilled artisan. Appellants, moreover, fail to show how applying a level of ordinary skill that requires experience with DPP-IV inhibitors or type II diabetes drugs would have remedied its failures of proof. While motivation and reasonable expectation of success need not be expressly disclosed by the prior art itself and may instead come from the background knowledge of the skilled artisan, merely asserting that a given modification would have been obvious to a skilled artisan does not make it so.

CONCLUSION

Because we conclude that the district court did not clearly err in finding that a skilled artisan would not have been motivated to make the proposed scaffold and isosteric replacements with a reasonable expectation of success, we need not reach the parties' remaining arguments. For the foregoing reasons, we affirm the district court's judgment upholding the validity of claims 4 and 12 of the '689 patent.

AFFIRMED